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Treatment of Severe Aplastic Anemia With an Immunosuppressive Agent Plus Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor and Erythropoietin

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To evaluate the therapeutic potential of hematopoietic growth factors (HGFs) during immunosuppressive treatment (IST) of severe aplastic anemia (SAA), 38 patients with newly diagnosed SAA received IST alone (group I), or IST plus recombinant human erythropoietin and granulocyte-macrophage colony-stimulating factor (rhEPO + rhGM-CSF) (group II). Eleven patients in each group received antilymphocyte globulin (ALG) for IST, and eight patients in each group received cyclosporine (CSA). Complete remission rates at one year were 26% and 74% for group I and group II patients, respectively. The ALG-treated subgroup showed the greatest differences between treatments. Compared with patients receiving ALG alone, patients treated with ALG plus HGFs had significantly better one-year survival (100% vs. 54.5%, $P < 0.05$), complete remission rates (91% vs. 36%, $P < 0.05$), more rapid and complete hematologic recovery, greater reductions in transfusion requirements, and lower infection rates. The data suggest a potential role for rhEPO + rhGM-CSF therapy in SAA patients receiving IST. Am. J. Hematol. 59:185–191, 1998. © 1998 Wiley-Liss, Inc.

Key words: aplastic anemia; hematopoietic growth factors; immunosuppressive agents; granulocyte-macrophage colony-stimulating factor; epoietin alpha

INTRODUCTION

Severe aplastic anemia (SAA) is a rare disease characterized by pancytopenia and a hypoplastic bone marrow [1]. Until the 1970s, clinicians had little to offer patients with SAA beyond blood transfusions or androgens, and the illness was usually fatal within one year [2]. The prognosis has improved, however, with the advent of allogeneic bone marrow transplantation and immunosuppressive therapy (IST). Survival rates following transplantation now average 65–75% at five years [3,4], although the procedure is restricted to younger patients (usually less than 45–50 years old) who have a human leukocyte antigens (HLA)-identical sibling (about 25% of candidates). The alternative treatment is IST, generally with cyclosporine (CSA), antilymphocyte globulin (ALG), or antithymocyte globulin (ATG), which produces hematologic response rates of 40–50% [3,4,5,6]. In the last few years, IST protocols have combined ALG or ATG with cyclosporine to achieve response rates of 60–70% in patients with SAA [7,8]. Despite this progress, the treatment of SAA still presents a therapeutic challenge even to experienced clinicians.

Another recent avenue of investigation involves the hematopoietic growth factors (HGFs). Recombinant granulocyte-macrophage colony-stimulating factor (rhGM-CSF) was first used to treat patients with SAA in the late 1980s [9]. Subsequent results were equivocal. In the studies of Vadan-Raj et al. [10], Nissen et al. [11], Antin et al. [12], and Champlin et al. [13], a total of 32 patients with moderate-to-severe aplastic anemia received rhGM-CSF at doses of 1.5–64 μg/kg/d, either

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TABLE I. Pretreatment Patient Characteristics*

Parameter	Group I (no growth factors)[a]		Group II (rhEPO + rhGM-CSF)[a]	
	Group IA (ALG) (n = 11)	Group IB (CSA) (n = 8)	Group IIA (ALG) (n = 11)	Group IIB (CSA) (n = 8)
Age (year)	32 (21–67)	26 (9–45)	34 (23–63)	28 (12–42)
Sex				
Male (n, %)	11 (100%)	6 (75%)	11 (100%)	6 (75%)
Female (n, %)	0	2 (25%)	0	2 (25%)
Peripheral counts				
Hemoglobin (g/L)	68 (54–78)	62.5 (67–88)	65 (43–74)	59 (36–80)
WBC ($\times 10^9$/L)	1.8 (1.7–3.3)	2.0 (1.7–3.3)	1.3 (1.2–2.1)	2 (1.4–2.8)
ANC ($\times 10^9$/L)	—	0.41 (0.38–0.8)	—	0.40 (0.32–0.72)
Platelets ($\times 10^9$/L)	14.6 (11–22)	14.7 (16–32)	10 (8–20)	11 (18–28)
Reticulocytes ($\times 10^9$/L)	3.2 (0–10)	9.6 (0–21)	0.32 (0–7.6)	5 (0–12.4)
Bone marrow histology				
Myelocytes (%)	16.2 (12–20.5)	23.1 (15–30.5)	12.4 (11–35.5)	26 (13–36.5)
Erythrocytes (%)	7.3 (0.5–29)	14.6 (10.5–29)	6 (0–25)	13.5 (9–25)
Megakaryocytes (number/smear)	1.0 (0–1)	0.5 (0–3)	0 (0–20)	1 (0–2)
Aplastic cellularity	11 (100%)	8 (100%)	11 (100%)	8 (100%)
Transfusion requirements				
RBC (mL/month)	863 (400–1000)	820 (800–1200)	1133 (400–1200)	625 (600–800)
Platelets (units/month)	60 (32–64)	31.7 (16–48)	76 (48–96)	43 (16–48)

*rhEPO, recombinant human erythropoietin; rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; ALG, antilymphocyte globulin; CSA, cyclosporine; WBC, white blood cell; ANC, absolute neutrophil count; RBC, red blood cell.
[a]Median (range).

intravenously (most patients) or subcutaneously. A transient increase in circulating neutrophils occurred in 29 patients (92%), with the median peak absolute neutrophil count (ANC) exceeding 1,000/mm^3 in 20 patients (67%). Eosinophil and monocyte counts also increased transiently in some patients, but red blood cell and platelet responses were rare. Most recently, rhG-CSF or rhGM-CSF has been administered for a more prolonged period to patients receiving IST, with very encouraging results [14,15].

There is limited experience with the use of recombinant human erythropoietin (rhEPO) in SAA. Most investigations of rhEPO have focused on myelodysplastic syndrome [16] and other refractory anemias [17], with somewhat disappointing results. However, further insights into the cellular actions of cytokines suggested that rhEPO might act synergistically with G-CSF or rhGM-CSF to enhance erythropoiesis and bone marrow restoration in patients with SAA [18]. Subsequent reports described clinical responses to rhEPO and either rhGM-CSF or G-CSF in some patients with moderate, severe, or refractory AA [19,20]. However, experience with the use of rhEPO plus rhGM-CSF in SAA patients receiving IST is confined to a single case report describing the successful treatment of an ALG-refractory patient with CSA, G-CSF, and rhEPO [21].

We therefore undertook this case-controlled study to evaluate the potential benefits of administering rhEPO and rhGM-CSF with IST to newly diagnosed patients with SAA.

PATIENTS AND METHODS

Patient Selection

Thirty-eight patients with newly diagnosed SAA were enrolled in this study. The criteria for SAA were those established by Camitta et al. [22] and included bone marrow hypoplasia (cellularity less than 25%) and at least two of the following three laboratory abnormalities: a corrected reticulocyte count below 1%; an ANC less than 0.5×10^9/L, and a platelet count less than 20×10^9/L.

All patients received immunosuppressive treatment, either alone (group I) or in combination with the HGFs, rhEPO and rhGM-CSF (group II). In group I, 11 patients received ALG as the immunosuppressive agent (group IA), and eight patients received CSA (group IB). In group II, 11 patients received ALG plus rhEPO and rhGM-CSF (group IIA), whereas eight patients received CSA plus rhEPO and rhGM-CSF (group IIB). All patients were grouped randomly, and consented to this study approved by the institutional committee for medical care and safety.

Table I displays the pretreatment clinical characteristics of the study population. The 38 patients ranged in age from nine to 67 years, and 34 of them (94.7%) were men. The patients who received ALG alone (group IA) or ALG in combination with rhEPO and rhGM-CSF (group IIA) were comparable in age, gender, and baseline disease severity. Likewise, the clinical characteristics of the patients in the two CSA groups (groups IB and IIB) were quite similar.

Treatment Plan

ALG regimen. Equine ALG (HALG, lymphoglobulin, Merieux, Lyon, France), 12 mg/kg/d, was administered by slow intravenous infusion on days one through five. Oral prednisone, one mg/kg/d, was administered on days 1–15, with rapid tapering of the dose over the next two weeks (days 15–30).

CSA regimen. CSA (Sandoz Pharmaceuticals Corp., Basel, Switzerland), five mg/kg/d given orally and in three equal divided doses, was started on day one and continued until at least day 90. The patients' plasma levels of CSA were not measured.

rhEPO and rhGM-CSF. Treatment with both cytokines was initiated on day 31 of the ALG regimen (group IIA) or day one of the CSA regimen (group IIB). RhGM-CSF (Schering-Plough, Ireland), 300 μg subcutaneously, was administered three times per week for the first month, twice per week during the second month, and once per week during the third month. rhEPO (Amgen, Inc., Thousand Oaks, CA), 6,000 units, was administered by intravenous infusion three times per week for the first month, twice per week during the second month, and once per week during the third month.

Other medications. All 38 patients received testosterone propionate (Triolandren®, Ciba Geigy, Basle, Switzerland), 250 mg intramuscularly (IM) twice per week, vitamin B_{12}, 500 μg IM once per week, and folic acid, 30 mg/d orally. None of the patients showed lower serum level of vitamin B_{12} or folic acid before the treatment.

Clinical and Laboratory Studies

Patients were evaluated at baseline and after three months of treatment. At each evaluation, clinical assessments were performed, and a complete blood count (CBC), platelet count, and bone marrow aspiration and biopsy were obtained. Clinical assessments included determinations of red cell and platelet transfusion requirements, infectious complications, and overall response rates. At one year, complete remission rates were ascertained for all patients.

Response Criteria

The criteria proposed by the Chinese Aplastic Anemia Working Party were used to classify hematologic responses as complete, partial, or absent. Complete responses were defined as transfusion-independent, with a hemoglobin level greater than 120 g/L, a neutrophil count greater than 1.5×10^9/L, and a platelet count greater than 80×10^9/L. Partial responses were defined as transfusion-independent with a hemoglobin level greater than 80 g/L, a neutrophil count greater than 0.5×10^9/L, and a platelet count greater than 20×10^9/L. Persistence of transfusion requirement was evidence of absent response.

Statistical Analysis

All 38 patients were included in the evaluation of treatment responses at three months and complete responses at one year. Treatment responses included survival rates, overall response rates, platelet and red cell transfusion requirements, peripheral blood cell counts, and selected bone marrow parameters. These parameters were also evaluated at one year in the patients receiving ALG (groups IA and IIA). Student's tests and paired t test were used to assess differences between treatment groups in transfusion requirements, peripheral blood cell counts, and bone marrow cell counts, whereas chi-square tests were used to compare dichotomous variables such as infection rates and response rates.

RESULTS

Survival Rates

Survival at three months (Table II) was 100% for the 11 patients who received ALG plus rhEPO and rhGM-CSF (group IIA) and 90.9% for the 11 patients who received ALG alone (group IA). At one year, however, 100% of group IIA patients, but only 54.5% of group IA patients, were still alive ($P < 0.05$, Table III).

All 16 patients treated with CSA (group IB and IIB) were alive at three months (Table IV). At one year, survival rates were 37.5% and 50% respectively for group IB and group IIB patients ($P > 0.05$, Table V).

Response Rates

At one year, the complete remission rate was 74% for the 19 patients who received rhEPO + rhGM-CSF in addition to ALG or CSA. In contrast, only 26% for the 19 patients who received ALG or CSA alone had a complete remission at one year ($P < 0.05$). The difference in complete response rates was more evident in the patients treated with ALG than in those treated with CSA.

Table II presents overall response rates at three months for the patients treated with ALG. All of the patients who received rhEPO + rhGM-CSF in addition to ALG (group IIA) responded to treatment compared with 45.5% of the patients receiving ALG alone ($P < 0.05$). Differences between the ALG groups were even more pronounced at one year. Complete remissions were evident in 90.9% of the patients receiving growth factors and 36.4% of the patients receiving ALG alone ($P < 0.05$).

Compared with the ALG cohorts, the CSA-treated patients (Table IV) had fewer responders at three months (four of eight patients in group IIB and 11 of 11 patients in group IIA) and fewer complete remissions at one year (three of eight patients in group IIB and 10 of 11 patients in group IIA).

TABLE II. Treatment Results at Three Months: Patients Who Received ALG Therapy*

Parameter	Group IA[a] (no growth factors) (n = 11)	Group IIA[a] (rhEPO + rhGM-CSF) (n = 11)	*P* value for difference
Survival rate (n, %)	10 (90.9%)	11 (100%)	
Response rate (n, %)	5 (45.5%)	11 (100%)	<0.05
Peripheral counts			
Hemoglobin (g/L)	77 (64–84)	91 (76–106)	<0.05
WBC ($\times 10^9$/L)	2.0 (1.4–2.6)	4.6 (2.9–5.8)	<0.05
ANC ($\times 10^9$/L)	0.78 (0.38–1.0)	2.8 (0.82–3.5)	<0.01
Platelets ($\times 10^9$/L)	32 (16–45)	48 (28–60)	
Reticulocytes ($\times 10^9$/L)	16.6 (6.2–61)	28.3 (16.2–61)	<0.05
Bone marrow histology			
Myelocytes (%)	30 (11–48)	51 (23–80.1)	<0.01
Erythrocytes (%)	21.6 (14.5–32)	26.5 (9–29.5)	
Megakaryocytes (number/smear)	3 (0–7)	9 (0–16)	
Normal cellularity	8 (73%)	11 (100%)	
Transfusion requirements			
RBC (mL/month)	563 (0–600)	150 (0–400)	
Platelets (units/month)	28 (16–32)	4 (0–16)	

*See Table I.
[a]Median (range).

TABLE III. Treatment Results at One Year: Patients Who Received ALG Therapy*

Parameter	Group IA[a] (no growth factors) (n = 11)	Group IIA[a] (rhEPO + rhGM-CSF) (n = 11)	*P* value for difference
Survival rate (n, %)	6 (54.5%)	11 (100%)	<0.05
Complete remissions (n, %)	4 (36.4%)	10 (90.9%)	<0.05
Peripheral counts			
Hemoglobin (g/L)	100 (94–124)	149 (127–178)	<0.05
WBC ($\times 10^9$/L)	3.6 (3.2–4.8)	6.2 (3.8–7.2)	<0.05
ANC ($\times 10^9$/L)	1.8 (1.4–2.6)	4.2 (2.1–5.8)	<0.01
Platelets ($\times 10^9$/L)	68 (48–88)	132 (78–176)	<0.05
Reticulocytes ($\times 10^9$/L)	34 (26–48)	58 (28.4–81.6)	<0.05
Bone marrow histology			
Myelocytes (%)	46 (43–54)	52 (34–68)	
Erythrocytes (%)	22 (22–26)	32.5 (19.5–49)	
Megakaryocytes (number/smear)	10 (6–24)	38 (13–65)	<0.05
Normal cellularity	2 (18.2%)	2 (18.2%)	<0.05
Hypercellularity	4 (36.4%)	9 (81.8%)	

*See Table I.
[a]Median (range).

Transfusion Requirements at Three Months

At three months, the ALG-treated patients had substantially lower red blood cell and platelet transfusion requirements (Table II) than they had at baseline (Table I) ($P < 0.05$). The reductions were almost twice as great in the patients who received rhEPO + rhGM-CSF (group IIA) compared with the patients who received ALG alone (group IA). In group IIA, median pretreatment red blood cell transfusion requirements decreased 87% (from 1,133 to 150 m/L per month) ($P < 0.05$), whereas median pretreatment platelet requirements declined 95% (from 76 to four units/month) ($P < 0.01$). In group IA, however, median pretreatment red blood cell transfusion requirements decreased 35% (from 863 to 563 m/L per month) ($P > 0.05$) and median pretreatment platelet requirements declined 54% (from 60 to 28 units/month) ($P > 0.05$).

The CSA-treated patients also showed substantial reductions in pretreatment transfusion requirements at three months (Table IV), but the differences between treatments were less apparent than with ALG. In the patients who received CSA plus growth factors (group IIB), the median pretreatment red blood cell transfusion requirements decreased 56% (from 625 to 275 mL/month), whereas median pretreatment platelet transfusion requirements declined 72% (from 43 to 12 units/month). In comparison, the median pretreatment red blood cell transfusion requirements of the patients who received CSA alone (group IB) decreased 57%

TABLE IV. Treatment Results at Three Months: Patients Who Received CSA Therapy*

Parameter	Group IB[a] (no growth factors) (n = 8)	Group IIB[a] (rhEPO + rhGM-CSF) (n = 8)	*P* value for difference
Survival rate (n, %)	8 (100%)	8 (100%)	
Response rate (n, %)	2 (25%)	4 (50%)	
Peripheral counts			
Hemoglobin (g/L)	77 (72–90)	86.5 (76–112)	
WBC ($\times 10^9$/L)	2.6 (2.1–3.6)	3.6 (2.4–6.8)	<0.05
ANC ($\times 10^9$/L)	0.58 (0.46–1.6)	1.4 (0.88–3.4)	<0.05
Platelets ($\times 10^9$/L)	23.5 (24–46)	30.3 (38–54)	
Reticulocytes ($\times 10^9$/L)	19.5 (6–24)	22.6 (10–48)	
Bone marrow histology			
Myelocytes (%)	30 (18.5–38.5)	45 (22.5–56.5)	<0.01
Erythrocytes (%)	18 (12.5–32.4)	23.4 (16.6–45)	
Megakaryocytes (number/smear)	1 (0–3)	3 (0–8)	
Normal cellularity	3 (37.5%)	6 (75%)	
Transfusion requirements			
RBC (mL/month)	350 (0–600)	275 (0–400)	
Platelets (units/month)	13 (0–32)	12 (0–16)	
Complete remissions at one year (n, %)	1 (12.5%)	3 (37.5%)	

*See Table I.
[a]Median (range).

TABLE V. Treatment Results at One Year: Patients Who Received CSA Therapy*

Parameter	Group IB[a] (no growth factors) (n = 8)	Group IIB[a] (rhEPO + rhGM-CSF) (n = 8)	*P* value for difference
Survival rate (n, %)	3 (37.5%)	4 (50.0%)	
Complete remissions (n, %)	1 (12.5%)	3 (37.5)	
Peripheral counts			
Hemoglobin (g/L)	87.3 (62–110)	102.8 (74–113.6)	
WBC ($\times 10^9$/L)	3 (2.4–4.2)	4 (2.6–6.68)	<0.05
ANC ($\times 10^9$/L)	1.4 (1.0–2.2)	2 (1.4–2.9)	<0.01
Platelets ($\times 10^9$/L)	45 (25–140)	68.8 (34–135)	
Reticulocytes ($\times 10^9$/L)	17.3 (8–22)	18.8 (14–28)	
Bone marrow histology			
Myelocytes (%)	32 (28–34)	40 (32–45)	
Erythrocytes (%)	20 (12–24.5)	24.5 (10.5–38)	
Megakaryocytes (number/smear)	4 (1–9)	9 (2–18)	
Normal cellularity	1 (12.5%)	3 (37.5%)	
Hypercellularity	2 (25.0%)	1 (12.5%)	

*See Table I.
[a]Median (range).

(from 820 to 350 mL/month), and median pretreatment platelet requirements declined 59% (from 31.7 to 13 units/month).

Peripheral Blood Cells

In general, changes in hemoglobin concentrations and peripheral blood cell counts mirrored response rates. Within the ALG-treated groups, the patients who received rhEPO + rhGM-CSF had statistically significantly higher median hemoglobin concentrations and white blood cell (WBC), neutrophil, and reticulocyte counts than did the patients who received ALG alone, both at three months (Table II) and one year (Table III). The most pronounced difference between the groups was in ANC ($P < 0.01$ at both three months and one year), whereas the difference between groups in platelet counts reached statistical significance only at one year. The median hemoglobin concentration of the patients who received rhEPO + GM-CSF increased from 65 g/L at baseline, to 91 g/L at three months, and to 149 g/L at one year. In contrast, the corresponding values for the patients who did not receive rhEPO were 68, 77, and 100 g/L.

As might be anticipated from the data on response rates and transfusion requirements, differences in the hematologic recovery of patients who received CSA with growth factors vs. CSA alone were less pronounced (Table IV). At the three month evaluation, the only cell

counts that were significantly higher in the group who had received rhEPO + rhGM-CSF were the ANC and WBC counts. The changes in hemoglobin concentration in the CSA-treated groups were similar in magnitude to those seen in the ALG groups at three months, but the difference did not reach statistical significance in the CSA patients.

Bone Marrow Changes

All patients had aplastic bone marrow before treatment. At three months, recovery of normal bone marrow cellularity was observed in 100% of the patients treated with ALG plus rhEPO + rhGM-CSF (group IIA) and 77% of the patients treated with ALG alone (group IA). At one year, bone marrow histology was hypercellular in 82% of group IIA patients and 36% of group IA patients ($P < 0.05$), normocellular in 18% of patients in each group, and aplastic in 0% of group IIA patients and 45% of group IA patients (Table III). The median number of megakaryocytes in the marrow was significantly greater in group IIA than in group IA at one year.

In the CSA-treated patients, normal bone marrow cellularity was restored at three months in six of eight patients (75%) who received growth factors and in three of eight patients (37.5%) who received CSA alone. As with the ALG-treated patients, the percentage of myelocytes in the bone marrow was significantly greater at three months in the growth factor-treated group.

Infections

Infectious complications were less common in the growth factor-treated patients. In the ALG-treated patients, infections developed in 0% of the patients receiving rhEPO + rhGM-CSF and 50% of the patients receiving ALG alone. In the CSA-treated patients, infections developed in 12.5% of the patients receiving rhEPO + rhGM-CSF and 50% of the patients receiving CSA alone.

Toxicity and Adverse Events

Overall, the addition of rhEPO + rhGM-CSF to the ALG and CSA treatment regimens was well tolerated. Four of the 19 patients (21%) who received growth factors experienced low-grade fevers during rhEPO + rhGM-CSF administration. The fevers resolved within 3–4 hr without specific treatment. Subcutaneous lymphadenopathy developed in two patients (10.5%) but did not require therapy.

DISCUSSION

To our knowledge, this study is the first to demonstrate a therapeutic benefit of rhEPO and rhGM-CSF in SAA patients receiving IST. Complete remission rates at one year occurred in 74% of the patients receiving IST and growth factors compared with 26% of the patients receiving IST alone. In the subgroup of patients who received ALG, the addition of rhEPO + rhGM-CSF was associated with significantly better one-year survival (100% vs. 54.5%, $P < 0.05$), higher complete remission rates (91% vs. 36%, $P < 0.05$), more rapid and complete hematologic recovery, greater reductions in transfusion requirements, and lower infection rates. At three months, the addition of rhEPO + rhGM-CSF produced a bilineage response in the ALG-treated patients, whereas at one year, a trilineage response was clearly evident. In the subgroup of patients who received CSA, the responses to rhEPO + rhGM-CSF were not as marked as those seen during ALG treatment. However, compared with patients who received CSA alone, the patients who received CSA plus growth factors had fewer infectious complications, a significant improvement in granulocyte counts, and there was an increase in the number of patients with return of normal bone marrow cellularity at three months. A too low dosage of CSA could not be excluded as the reason the CSA group had less response than the ALG group.

The response rates observed for the patients who received ALG alone are in agreement with those reported for ALG by others [3,4]. However, the response rates for the patients who received ALG with growth factors are comparable to those recently reported for intensive immunosuppression regimens that administer both ALG and CSA [3,8,14]. Although the number of patients receiving ALG and growth factors in this study is small, the data are intriguing and warrant further evaluation.

The favorable responses to rhEPO + rhGM-CSF may be explained by the synergistic activities of two growth factors. rhGM-CSF induces the proliferation of granulocyte-macrophage progenitor cells (CFU-GM), stimulates megakaryocyte progenitor cells to response to thrombopoietin, interacts with EPO to stimulate production and differentiation of immature erythroid progenitor cells (BFU-E), acts synergistically with other growth factors to augment the expansion of very primitive hematopoietic progenitor cells, and enhances the function of mature granulocytes and macrophages [23,24]. In addition, rhEPO may have thrombopoietin-like activity [25]. Our data suggest that hematopoietic progenitor cells are still present in many patients with SAA and that they are capable of responding to growth factors when the destructive effects of immunologic processes are suppressed. As suggested by Champlin et al. [13], the addition of cytokines, which act on the early stem cell (e.g., IL-3, IL-1 or IL-6, etc.) and those which act primarily as differentiating factors (e.g., EPO, G-CSF, GM-CSF, and C-MPL ligand), might improve the effectiveness of IST in unresponsive patients.

Other factors probably contributed to the favorable response rates in this study. The route of administration for rhGM-CSF was subcutaneous, which prolongs the half-life of rhGM-CSF, enhances its effects on leukocytes, and lessens its toxicities compared with intravenous administration [26,27]. We also treated patients

with the growth factors for several months unlike the earlier, less favorable studies of rhGM-CSF in SAA that generally limited treatment to 7–14 days [10–12]. Recent data have shown that rhGM-CSF produces more sustained ANC responses when it is administered for a longer period [28,29].

Minimal toxicity and adverse events were associated with the administration of rhEPO + rhGM-CSF in our patients. However, it has been suggested that the use of HGFs with IST may increase the risk of late complications such as myelodystrophic syndromes and acute leukemia with monosomy 7 [30]. Further follow-up with be required to assess the incidence of late complications following treatment of SAA with IST and growth factors.

In summary, our study suggests that patients with SAA may benefit from the administration of rhEPO and rhGM-CSF during treatment with IST. However, the exact role of growth factors in the treatment of SAA is still uncertain, and further studies with longer follow-up are needed.

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